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Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children (Review)

Bradford NK, Edwards RM, Chan RJ

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[Intervention Review]

Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children

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ABSTRACT

Background

Guidelines and clinical practice for the prevention of complications associated with central venous catheters (CVC) around the world vary greatly. Most institutions recommend the use of heparin to prevent occlusion, however there is debate regarding the need for heparin and evidence to suggest 0.9% sodium chloride (normal saline) may be as effective. The use of heparin is not without risk, may be unnecessary and is also associated with increased cost.

Objectives

To assess the clinical effects (benefits and harms) of intermittent flushing of heparin versus normal saline to prevent occlusion in long term central venous catheters in infants and children.

Search methods

The Cochrane Vascular Trials Search Co-ordinator searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (Issue 3, 2015). We also searched the reference lists of retrieved trials.

Selection criteria

Randomised controlled trials that compared the efficacy of normal saline with heparin to prevent occlusion of long term CVCs in infants and children aged up to 18 years of age were included. We excluded temporary CVCs and peripherally inserted central catheters (PICC).

Data collection and analysis

Two review authors independently assessed trial inclusion criteria, trial quality and extracted data. Rate ratios were calculated for two outcome measures - occlusion of the CVC and central line-associated blood stream infection. Other outcome measures included duration of catheter placement, inability to withdraw blood from the catheter, use of urokinase or recombinant tissue plasminogen, incidence of removal or re-insertion of the catheter, or both, and other CVC-related complications such as dislocation of CVCs, other CVC site infections and thrombosis.

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Main results

Three trials with a total of 245 participants were included in this review. The three trials directly compared the use of normal saline and heparin, however, between studies, all used different protocols for the standard and experimental arms with different concentrations of heparin and different frequency of flushes reported. In addition, not all studies reported on all outcomes. The quality of the evidence ranged from low to very low because there was no blinding, heterogeneity and inconsistency between studies was high and the confidence intervals were wide. CVC occlusion was assessed in all three trials (243 participants). We were able to pool the results of two trials for the outcomes of CVC occlusion and CVC-associated blood stream infection. The estimated rate ratio for CVC occlusion per 1000 catheter days between the normal saline and heparin group was 0.75 (95% CI 0.10 to 5.51, two studies, 229 participants, very low quality evidence). The estimated rate ratio for CVC-associated blood stream infection was 1.48 (95% CI 0.24 to 9.37, two studies, 231 participants; low quality evidence). The duration of catheter placement was reported to be similar between the two study arms, in one study (203 participants).

Authors' conclusions

The review found that there was not enough evidence to determine the effects of intermittent flushing of heparin versus normal saline to prevent occlusion in long term central venous catheters in infants and children. Ultimately, if this evidence were available, the development of evidenced-based clinical practice guidelines and consistency of practice would be facilitated.

PLAIN LANGUAGE SUMMARY

Replacing heparin with saline to prevent complications in long term central venous catheters in children

Background

A central venous catheter (CVC) is a long, thin, flexible tube which is inserted into a large central vein. This enables access to the blood stream for people with serious medical conditions to receive medications and fluids, as well as the collection of blood specimens. Long term central venous catheters are used to access the blood system in children with complex medical conditions like cancer. To stop the catheter from becoming blocked it is usual to use heparin, a drug that prevents clots forming, to flush the catheter. However, some studies have shown that heparin is not necessary, and that normal saline (a sterile salt water solution) can be safely used instead. Heparin may be associated with complications, such as bleeding and infection, along with higher costs for health care providers. While the complications such as infections and occlusions are uncommon, practices vary around the world and there are many inconsistencies regarding the best flush solution to use to prevent complications in long term catheters.

Study characteristics and key results

This review included randomised controlled trials, (clinical studies where people were randomly assigned into one of two or more treatment groups), that compared the use of saline and heparin to prevent blockage, and other complications related to long term catheters. The evidence is current to April 2015. Two review authors independently reviewed the studies. Three studies with a total of 245 participants were included in the review. The three trials directly compared the use of saline and heparin, however, between studies, all were very different in the way they compared saline and heparin, with different concentrations of heparin and different frequency of flushes reported. We were able to combine the results of two studies; the analysis showed imprecise results for the blocking of catheters and blood stream infections between normal saline and heparin. One study reported the duration of catheter placement to be similar between the two study arms.

Quality of the evidence

The overall quality of the evidence ranged from low to very low. There was high risk of bias for blinding, there were differences between the studies methods and interventions, inconsistent results between the studies, and not all studies reported all outcomes of interest. We found there was not enough evidence to determine which solution, heparin or saline, is more effective for reducing complications. Further research is required and is likely to have an important impact in this area.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Heparin versus normal saline flushing for prevention of occlusion in long term central venous catheters in infants and children

Patient or population: Infants and children with a long term central venous catheter
Settings: Tertiary hospitals
Intervention: Heparin flush
Control: normal saline flush

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control: normal saline flush	Comparison: Heparin flush				
CVC occlusion rate per 1000 catheter days Ability to infuse solution through CVC Follow-up: 3029 to 115, 991 at-risk days	**Study population**		**Rate ratio 0.75** (0.10 to 5.51)	229 (2 studies)	⊕◯◯◯ **very low**[2,3,4]	
	551 per 1000	**507 per 1000** (99 to 1000)				
	Moderate					
	549 per 1000	**505 per 1000** (99 to 1000)[1]				
CVC-associated blood stream infection rate per 1000 catheter days Incidence of positive blood culture Follow-up: 3029 to 115, 991 at-risk days	**Study population**		**Rate ratio 1.48** (0.24 to 9.37)	231 (2 studies)	⊕⊕◯◯ **low**[2,4,5,6]	
	93 per 1000	**209 per 1000** (103 to 425)				
	Moderate					
	98 per 1000	**220 per 1000** (109 to 447)[1]				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CVC**: Central venous catheter

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Moderate risk group was assumed based on the moderate risk for CVC occlusion and CVC-associated blood stream infection in the Cesaro 2009 study
[2] No blinding in either study. Peformance and detection bias is high in both studies
[3] Heterogeneity and inconsistency between studies is high
[4] Confidence intervals were wide and included the null hypothesis
[5] Results could be attributed to other factors associated with the use of heparin
[6] The outcomes could also be attributed to the use of positive pressure cap in the Cesaro 2009 study

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BACKGROUND

Description of the condition

A central venous catheter (CVC) is a long, thin, flexible tube which is inserted into a large central vein, with the tip of the catheter ideally placed within the superior vena cava (Schuster 2000). This enables the administration of medications and fluids, as well as the collection of blood specimens to avoid unnecessary venipunctures. CVCs are commonly known as 'central lines' or by their brand name including Broviac, Hickman, and Port-a-Cath. The use of long term CVCs for the management of chronic medical conditions in infants and children has greatly improved the quality and safety of care provision. Long term CVCs are typically inserted when the administration of intravenous medication or nutritional support is required over a considerable time period. Hypertonic medications such as vesicant chemotherapy drugs, certain antibiotics, other supportive drugs and parenteral nutrition, are not able to be safely administered through peripheral venous catheters. For children with cancer and other chronic medical conditions who require such medications, this safety issue is overcome by the insertion of a CVC which commonly remains in place for the duration of treatment (Gonzalez 2012). There are three types of long term CVCs: tunnelled catheters; totally implanted catheters; and peripherally inserted central catheters (PICC). A tunnelled CVC is surgically inserted under the skin, with the catheter lumen(s) typically exiting from the chest or neck. A totally implanted catheter is also surgically inserted, but is placed entirely under the skin and commonly referred to as a 'port'. The port reservoir is accessed with a needle through the skin. A PICC line is inserted into a central vein through the arm and thus is a narrower catheter.

Adverse events associated with CVCs may cause complications in up to 46% of children (Athale 2012). Adverse events in the scope of this review include mechanical failure, catheter fracture, infections and thrombotic complications, all of which can affect patient morbidity and mortality (Baskin 2009; Fratino 2005; Stocco 2012; Wong 2012). Mechanical failure is often attributed to catheter occlusion. Over time, it is common for a fibrin sheath to develop at the tip of the catheter. The fibrin sheath may prevent aspiration of blood from the catheter and cause resistance when infusing fluids. An intraluminal clot can also occur, which can totally occlude the catheter. Occlusion can result in the need for the catheter to be removed (and replaced), interrupting and delaying treatment of the underlying disease (Shah 2007). Occlusions of CVCs are estimated to occur in 14% to 36% of patients within one to two years of catheter insertion, (Fratino 2005) or at an incidence rate of 1.35 per 1000 catheter days (95% confidence interval (CI) 1.1 to 1.63) (Revel-Vilk 2010). Incidence rates of central line-associated blood stream infection differ depending upon the type of catheter, with rates reported between 1.40 per 1000 catheter days (95% CI 1.06 to 1.82) and 0.46 per 1000 catheter days (95% CI 0.29 to 0.69). Thrombotic complications are the rarest adverse events reported in children, with a lower incidence rate of 0.08 per 1000 catheter days (95% CI 0.04 to 0.16) (Fratino 2005).

Description of the intervention

A flush refers to solution of 0.9% sodium chloride being injected to clear the catheter of blood or fibrin build-up. This is commonly used when the catheter is accessed, between administration of medications, or before and after collection of blood specimens. A positive pressure lock is used when the catheter will not be accessed for a period of time, and refers to the technique used to ensure blood does not flow back into the catheter after it is flushed, which may otherwise clot and cause occlusion. Tunnelled CVCs and PICC lines are typically flushed and locked weekly, while implanted ports are flushed and locked every 4 to 6 weeks. A typical lock solution for tunnelled catheters in children is to use between 1 ml to 3 ml (depending on the volume of the catheter) of 10 units/ml of heparin for a 24-hour to 7-day lock. For implanted ports, 5 mL of 100 units/mL is typically used as a lock solution for a 30-day lock (Davis 2013). However, there is debate regarding the effectiveness of heparin to prevent occlusion over such time periods, given its short half-life (Young 2008). The evidence to support the use of heparin to prevent occlusion in adult CVCs is inconclusive and there is growing evidence to support the use of 0.9% sodium chloride (normal saline) to lock CVCs, particularly in the paediatric population (Bertoglio 2012; Lee 2005).

How the intervention might work

Heparin is used to prevent occlusion because of its anti-coagulant properties which are believed to prevent thrombus forming in the catheter. Alternatively normal saline, when used with pulsatile (push-pause rather than continuous) flushing techniques and a positive pressure lock or positive displacement device, may be as effective in preventing thrombus formation in catheters - eliminating the need for heparin to be used.

Why it is important to do this review

Cathter maintenance practices vary among institutions because of the lack of evidence regarding best practice to prevent occlusion of CVCs. Variations include the quantity of flush and lock solutions, the proportional volume of heparin lock solution, and the frequency of flushes and locks. The use of heparin is not risk free and in certain instances may actually cause harm, including infection (Shanks 2005) and heparin-induced thrombocytopenia (HIT) (Barclay 2012). The mechanism of haemostasis in children is different when compared to adults, particularly in infants and very young children, and the evidence suggest algorithms used in adults are unlikely to be valid in children (Monagle 2010). Additionally, treatments for diseases such as cancer involve the use of

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medications which can affect coagulation. In the absence of specific data related to pediatrics, using evidence based on adults may be inappropriate and there is a need for paediatric-specific studies (Monagle 2010). For these reasons the use of heparin to prevent CVC occlusion should be judicious and evidence-based. While the risks of adverse effects from the use of heparin may be regarded as less than the potential occlusion of a catheter and subsequent replacement, it is important to ensure interventions are based on evidence.

In the adult population, there have been several trials (Goossens 2013; Schallom 2012; Schilling 2006), a systematic review (Mitchell 2009), and a Cochrane Review of the use of heparin versus normal saline to prevent occlusions in CVCs (Lopez-Briz 2014). As evidence from adult studies is not directly transferable to paediatrics, a systematic review focused on infants and children is required. A review published in 2014 (Conway 2014), that did relate specifically to paediatrics, did not identify all relevant studies and made recommendations based on the current practice of several institutions. These recommendations were not evidence-based, and are contrary to the practice of many other institutions. Therefore, it is important to systematically appraise the evidence for the use of heparin compared with normal saline to prevent occlusion of central venous catheters.

OBJECTIVES

To assess the clinical effects (benefits and harms) of intermittent flushing of heparin versus normal saline to prevent occlusion in long term central venous catheters in infants and children.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials that compared the efficacy of heparin with normal saline for the prevention of occlusion of CVCs were considered for this review. Due to potential bias, we excluded studies that used alternative methods (quasi-randomised) to allocate participants to a control or intervention group.

Types of participants

The study population of interest comprised infants and children aged 0 to 18 years of age, who had a CVC (tunnelled catheter or totally implanted catheter), inserted for long term venous access. Because midline catheters are not placed in the same position as a CVC (superior or inferior vena cava), and PICC have narrow lumens which require specific care, studies of infants or children with midline catheters or PICCs were beyond the scope of this review and were excluded. There were no restrictions on the insertion site, or catheter tip placement site (superior or inferior vena cava). There were no restrictions on the healthcare setting in which the study was conducted, for example tertiary hospital or community setting. Where studies had a mixed population that included infants, children and adults, we included data from infants and children only. If information was not presented in the article, we contacted the study authors to attempt to obtain age-stratified results. If we were unable to contact the study authors, and children and infants comprised a proportion greater than 20% of the study population, we included the appropriate proportion of participants to represent the paediatric component. If we were unable to obtain any information regarding the proportion of infants and children in the study population, we excluded the study from the review.

Types of interventions

The intervention of interest was the intermittent (any time frequency) flushing of heparin (any dose or concentration) compared with intermittent flushing with normal saline (alone, or in combination with pulsatile flushing techniques, positive displacement devices or positive pressure lock) delivered with the intention to prevent occlusion of the CVC.

Types of outcome measures

Outcome measures were not considered a part of eligibility criteria.

Primary outcomes

- Occlusion of the CVC, determined by the inability to infuse fluids through the catheter.
- CVC-associated blood stream infection or colonisation of the catheter.
- Duration in days of catheter placement.

Secondary outcomes

- Inability to withdraw blood from the CVC.
- Any use of urokinase or recombinant tissue plasminogen such as alteplase.
- Incidence of removal/re-insertion of the catheter.
- Other CVC-related complication (e.g. dislocation of CVCs, thrombosis, tunnel or site infection, allergic reaction, haemorrhage, heparin-induced thrombocytopaenia, elevated hepatic enzymes.

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Search methods for identification of studies

No restrictions were placed on language.

Electronic searches

The Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (CRS) http://www.metaxis.com/CRSWeb/Index.asp (2015, Issue 3). See Appendix 1 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular module in the *Cochrane Library* (www.cochranelibrary.com).

The following trial databases were searched by the TSC in April 2015 for details of ongoing and unpublished studies using the terms heparin and sodium and (catheter or cannula or CVC or PICC):

- World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/
- ClinicalTrials.gov http://clinicaltrials.gov/
- Current Controlled Trials http://www.controlled-trials.com/

Searching other resources

Two review authors (NB, RE) screened the reference lists of retrieved articles for additional studies. We attempted to contact authors of any studies identified in unpublished literature to obtain further data.

Data collection and analysis

Selection of studies

Two review authors (NB, RE) independently reviewed all titles and abstracts of retrieved articles to assess eligibility against inclusion criteria. Where disagreement existed regarding the inclusion of a study, the third author (RC) was consulted. We obtained the full text of all potentially eligible studies and contacted authors of primary studies to clarify data if necessary. A flowchart based upon the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher 2009) statement was used to document results. We recorded data on the results of all searches undertaken including: database searched; date; limiters, and number of results.

Data extraction and management

Two review authors (NB, RC) extracted the data independently using the Cochrane Vascular Group forms for dichotomous and continuous data. Data were collected regarding the:

- lead author and year of study;
- country where the study was undertaken;
- participant inclusion criteria;
- participant age and gender;
- study design;
- description of interventions;
- setting of study;
- number of participants in each arm;
- attrition or losses to follow-up;
- outcome measures.

We resolved any disagreement regarding data extraction by discussion between all review authors (NB, RE, RC).

Assessment of risk of bias in included studies

We assessed bias within studies using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) and report the following domains: sequence generation; allocation concealment; blinding; incomplete data; selective outcome reporting, and other biases. If necessary, primary authors were contacted to clarify any information. Two review authors (NB, RC) independently undertook the risk of bias assessment. Disagreement regarding the assessment of bias was resolved by discussion between review authors (NB, RC).

Measures of treatment effect

As dichotomous outcomes such as occlusion or central line-associated blood stream infection could occur more than once for individual participants, we calculated count data per time at risk of outcome (per 1000 catheter days) and reported rate ratios with 95% confidence intervals (CI). Using section 9.4.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), we also calculated the formula for the log of the standard error for each rate ratio. Descriptive statistics including mean differences (MD) with 95% CI were used for any continuous data. We planned to report time-to-event data as hazard ratios (HR) with 95% CI. We analysed data with Review Manager software (RevMan) (RevMan 2014).

Unit of analysis issues

We identified the unit of analysis for each trial for intervention (normal saline) and control (heparin) groups. Where results were reported from cluster randomised controlled trials, cross-over trials or repeated measurements of the same outcome, we took the appropriate design effect into consideration to avoid unit of analysis error.

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Dealing with missing data

We contacted primary authors of studies to attempt to obtain any missing data. We assessed all data for potential mislabelling and made no assumptions regarding missing data in order to include these in the analysis. Where data were missing and not able to be obtained, we excluded them from the analysis.

Assessment of heterogeneity

Where feasible, we assessed heterogeneity between effect sizes of included studies by visual inspection of forest plots and the Chi ^{2} test (P value < 0.05). We planned to describe inconsistency between trials by assessing the I^2 statistic and the variability between the effect estimates (Higgins 2003), with an I^2 value of 50% considered to represent substantial heterogeneity (Higgins 2011). Additionally we considered the clinical heterogeneity of studies where the frequency of interventions, or catheter type differed between studies.

Assessment of reporting biases

Where appropriate, we planned to assess publication bias using funnel plots and Egger's tests (Egger 1997; Sterne 2011). Additionally, we reduced reporting bias by searching multiple electronic databases, proceedings of conferences and scientific meetings, and trial registries. We excluded duplicates of the same trial to avoid duplicate publication bias.

Data synthesis

The primary author (NB) entered data into RevMan (RevMan 2014) and undertook analysis according to recommended guidelines (Deeks 2011). We planned to combine effect sizes across studies using a fixed-effect model and confidence interval limits set at 95%. Where substantial heterogeneity existed, we pooled data using the random-effects model. Where it was not appropriate to combine results, we presented a narrative review descriptively summarising the results.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis where appropriate with: type of CVC (tunnelled catheter or implanted port); insertion site or catheter tip placement site, or both; age group; and diagnosis.

Sensitivity analysis

We planned to undertake sensitivity analyses to examine the effects of different trials and their methodology including; number of participants (greater than 50 versus fewer than 50 participants); and duration of follow up.

Summary of findings

We presented the main findings of the review results concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data for the primary outcomes CVC occlusion rate and CVC-associated blood stream infection in Summary of findings for the main comparison, according to Schünemann 2011 and Atkins 2004. The GRADEprofiler (GRADEpro) software was used to assist in the preparation of the 'Summary of findings' table (GRADEpro GDT 2015).

RESULTS

Description of studies

See Figure 1; Characteristics of included studies; Characteristics of excluded studies

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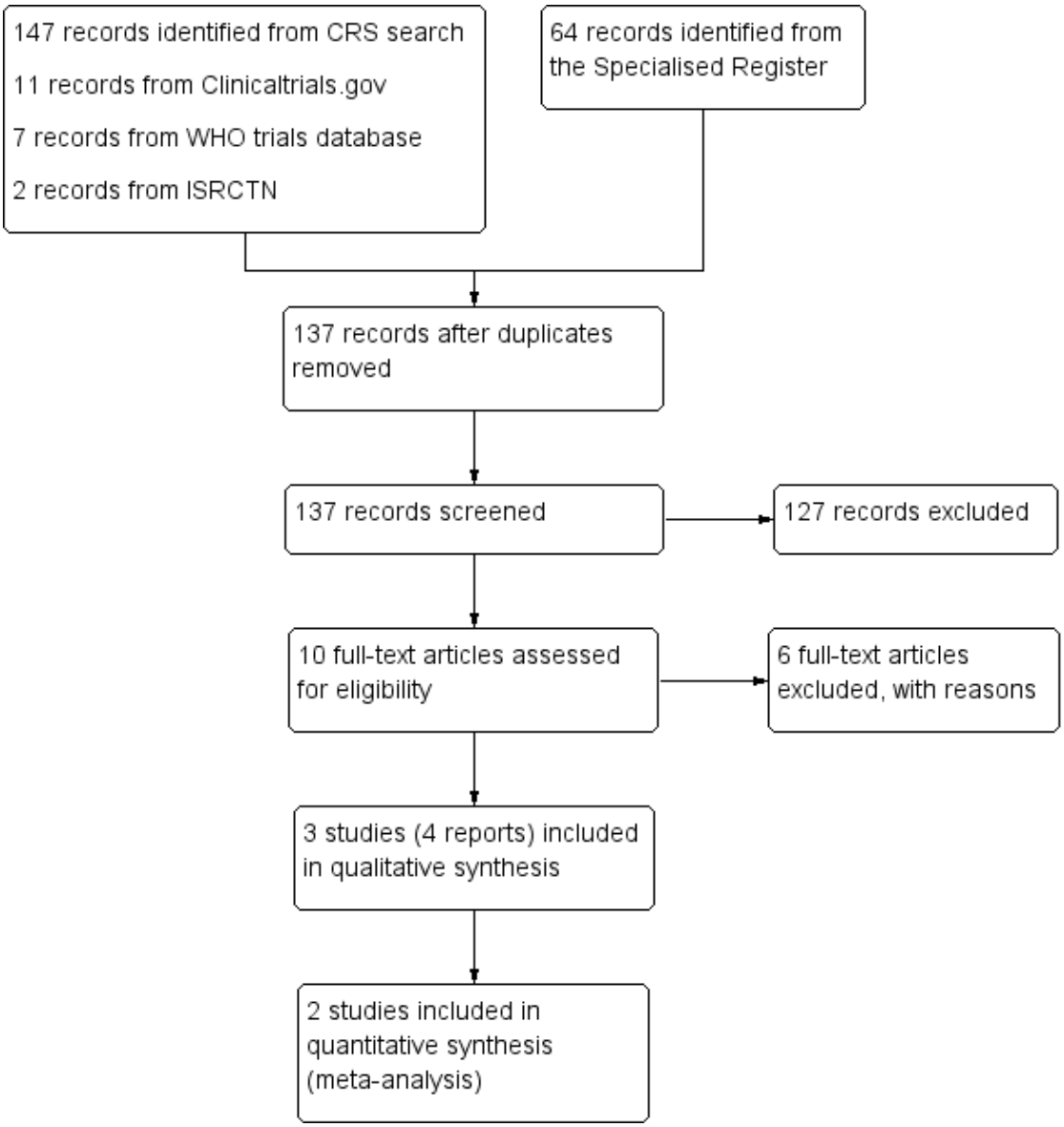
Figure 1. Study flow diagram.



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Results of the search

See Figure 1.

We contacted three individual study authors for further study details (De Neef 2002; Goossens 2013; Smith 1991) but we were unable to obtain further information regarding the Smith 1991 or De Neef 2002 studies. The authors of Goossens 2013 provided data for paediatric patients.

Included studies

Based on the review of full texts, three studies met eligibility criteria and were included in the final review (Cesaro 2009; Goossens 2013; Smith 1991) (see Table: Characteristics of included studies). The studies undertaken by Cesaro 2009 and Goossens 2013 were of medium duration (25 and 23 months respectively) and included a follow up periods of 14 and six months respectively. The Smith 1991 study was a cross-over study of two, three-and-a-half month time periods (total duration seven months) and did not include a follow-up period. We were not able to ascertain if this study was analysed as paired data or not, and no information was available regarding the first cross-over period. All studies had obtained ethical approval from their relevant institutions.

Population

The three included trials involved a total of 245 participants, with the majority of participants (203) coming from Cesaro 2009. From the other two studies, Goossens 2013 contributed 28 participants, and Smith 1991 contributed 14 participants. All participants had a long-term central venous catheter placed, and were undergoing treatment for haematology or oncology conditions. Cesaro 2009 was undertaken in Italy, Goossens 2013 in Belgium, and Smith 1991 in Canada. Participants in Smith 1991 and Cesaro 2009 had Broviac tunnelled CVCs inserted, whereas all participants in Goossens 2013 had totally inserted catheters (ports) placed. All studies were undertaken in developed nations in tertiary referral centres. Both Cesaro 2009 and Goossens 2013 undertook power size calculations to obtain sample sizes, however it is important to note that children comprised only 3.5% of the Goossens 2013 study population, thus this study was not powered to analyse the results of children separately.

Intervention

Participants in all three included studies received standard care except where stated as follows. All included studies involved an experimental arm where normal saline solution was used in place of standard solution (heparinised saline) when the CVC was not being used. As well as changing the type of solution used to flush the CVC, Smith 1991 increased the duration between flushes in the intervention arm. Participants in the standard arm received standard care with CVCs flushed twice daily. In the intervention arm, the duration between flushes was increased to weekly. Similarly, Cesaro 2009 increased the duration between flushes in the intervention arm compared to standard care from twice per week to weekly. Cesaro 2009 also introduced a positive pressure cap into the intervention arm. These changes confound the interventions so it is not possible to associate outcomes with the use of the solution alone. Goossens 2013 was the only study included in this review where the only difference between the intervention and standard arm was the use of normal saline (experimental) or heparin (standard) solution to flush the CVC under positive pressure.

Control

In all studies, participants randomised to the standard arm received various concentrations of heparinised saline to flush their CVC. Particpants in Smith 1991's study received 5 mL of 10 units/mL heparinised saline (i.e. 50 units of heparin) twice daily. Participants in Cesaro 2009's study received 3 mL of 200 units/mL heparinised saline (i.e. 600 units of heparin) twice weekly. In Goossens 2013's study, participants in the standard arm received maintenance care (normal saline pulsatile flushes after infusions, blood sampling etc), and their CVC was flushed with 3 mL of 100 units/mL heparin (i.e. 300 units of heparin) under positive pressure at least every eight weeks when the CVC was not in use.

Outcomes

The primary outcome of interest, occlusion of CVC, was measured in all three studies included in this review. In Smith 1991, occlusion was defined as blockage of the catheter and measured by both echocardiogram to determine thrombus formation and inability to infuse fluids. Smith 1991 also recorded CVC-associated blood stream and exit site infections. Blood stream infections were defined by Smith 1991 as the presence of systemic infection and positive blood cultures, and exit site infections were defined as the presence of infection and positive culture from the exit site. Cesaro 2009 defined CVC occlusion as the inability to withdraw blood or infuse fluids, or both. Cesaro 2009 also measured CVC-associated blood stream infection, CVC mechanical issues and CVC-related thrombosis. CVC-associated blood stream infection was defined by Cesaro 2009 as one or more positive blood cultures obtained through the CVC in patients with signs of infection. CVC mechanical issues included dislodgement of the CVC tip or cuff, fracture or accidental CVC self-removal by the patient; these outcomes were evaluated by visual inspection and chest X-ray. CVC-related thrombosis was measured where clinically indicated by ultrasound, computed tomography or magnetic resonance imaging.

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Goossens 2013 measured CVC occlusion as a secondary end point, their primary outcome was partial occlusion defined by easy infusion, difficulty withdrawing from CVC. Other secondary outcome measures in Goossens 2013 were CVC-associated blood stream infection and other CVC mechanical issues. CVC-associated blood stream infection was defined by Goossens 2013 as positive blood cultures from the CVC and peripheral veins, and fever or chills in the absence of other infection sources. CVC mechanical issues encompassed all other functional problems encountered with each access. As participants could experience outcomes more than once, all studies reported the number of catheter days that participants in either study arm were at risk of experiencing an outcome.

Excluded studies

Six studies were excluded from the review. None of the six excluded studies met eligibility criteria; Geritz 1992 and Schultz 2002 reported trials investigating peripheral catheters, De Neef 2002 and Kaneko 2004 studies investigated arterial catheters, and Pumarola 2007 and Rabe 2002 investigated temporary central venous catheters. Additionally , Kaneko 2004 and Rabe 2002 did not include children in their study population. See: Characteristics of excluded studies.

Risk of bias in included studies

See risk of bias: Figure 2 and Figure 3 and also Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

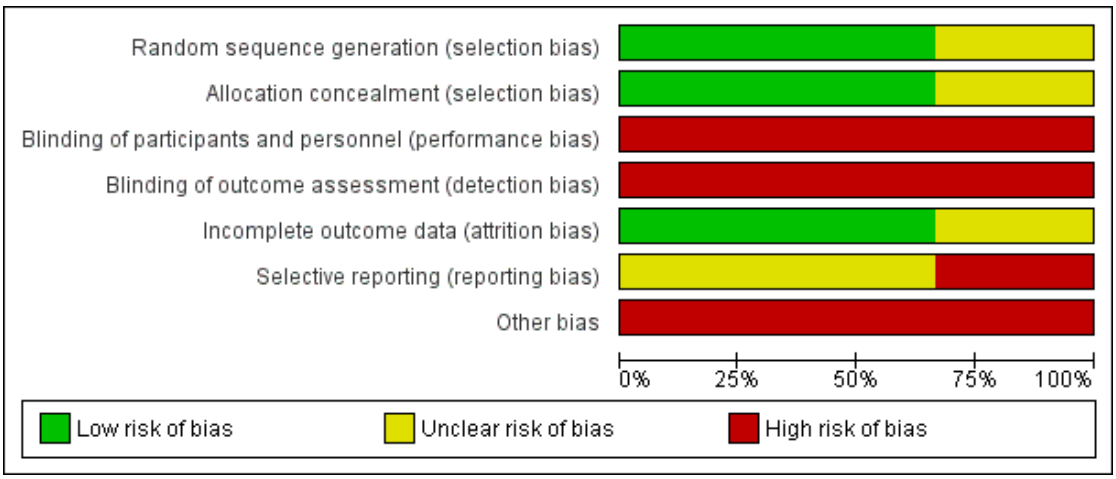

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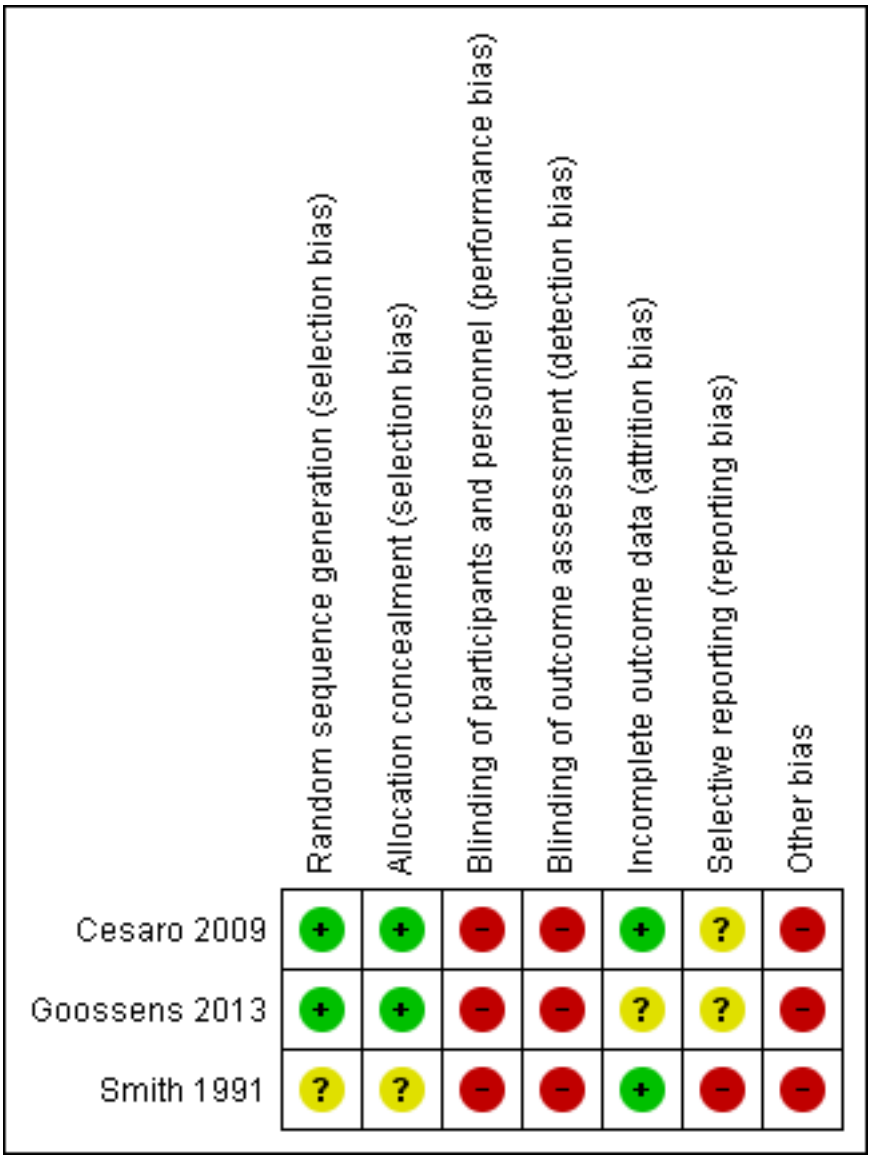
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

There was low risk of selection bias in the Cesaro 2009 and Goossens 2013 studies; these investigators reported using computerised random sequencing and concealing allocation until participants had been recruited and provided consent. Smith 1991's study did not provide any details regarding how participants were randomised and was therefore judged to be of unclear risk of selection bias.

Blinding

None of the three included studies blinded investigators, clinicians or participants regarding to which arm the participant had been allocated. Goossens 2013 stated blinding was not possible for logistical reasons. All outcomes were objectively measured, but in all three studies there is the possibility clinicians may have modified their technique depending on the arm to which the participant had been allocated. All studies were therefore assessed as a high risk of both performance and detection bias.

Incomplete outcome data

All three studies included in this review reported full results for all participants who were randomised. A flow chart of participant progress through the study was provided by Goossens 2013. There were no protocol violations reported by Goossens 2013 or Cesaro 2009. In Goossens 2013 there was a 4.9% drop-out rate which was not statistically different between the two groups and all analysis was based on intention-to-treat. This drop out rate relates to the adult participants and not the children included in this review. In Cesaro 2009 22% (n = 44) of CVCs required premature removal, however there were no statistical differences between study arms. Attrition of two participants due to death also occurred in this study but no losses to follow up occurred. Smith 1991 reported no losses to follow up. Cesaro 2009 and Goossens 2013 were assigned a low risk of attrition bias, and Smith 1991 an unclear risk.

Selective reporting

All studies reported on their primary and secondary outcome measures. There were no study protocols available for any studies, therefore reporting bias for all studies is unclear. Smith 1991 reported data in a basic format with no results from statistical tests. It is not clear if paired analysis was undertaken; this study was assessed at being at high risk for reporting bias.

Other potential sources of bias

In both the Cesaro 2009 and Smith 1991 studies, there is a high concern for confounding of results. Both these studies altered the frequency between flushes for the experimental arm as well as the experimental solution. Additionally in Cesaro 2009 the experimental arm included the use of a positive pressure cap. It is not possible therefore to attribute the outcome to the use of the solution alone, the outcome could plausibly also be attributed to the frequency of flushes or the use of a positive pressure cap. It may therefore be more appropriate to view the intervention as a component of a bundle of care. Further bias may exist in the subset of unpublished data of paediatric participants provided by Goossens 2013; we were not able to determine if the characteristics of this subset of participants were subject to other biases. As a cross over study there may have been a carry-over effect of the intervention from one arm to the other in Smith 1991. It is not clear if the study authors considered this. These other potential sources of bias across all three studies are substantial and reduce confidence in the results.

Effects of interventions

See: **Summary of findings for the main comparison** Heparin versus normal saline flushing for prevention of occlusion in long term central venous catheters in infants and children

See: Summary of findings for the main comparison for the two primary outcomes CVC occlusion and CVC-associated blood stream infection or colonisation. See Additional Table 1 for summary of outcome rates per 1000 catheter days.

As we were not able to ascertain if Smith 1991 analysed data as paired data or not, and no information was available regarding the first cross-over period, the results from this study were not pooled with the other studies..

Primary outcomes

Comparison: normal saline versus heparin

CVC occlusion (Analysis 1.1)

CVC occlusion was reported in all three included trials (243 participants; Goossens 2013 provided data for 26 of 28 participants for CVC occlusion). Smith 1991 and Cesaro 2009 provided information regarding the number of catheter days for each arm of their study. Goossens 2013 provided the mean catheter days for each arm of the total population in their study (i.e. including both the child and adult participants). We assumed that the mean number of catheter days for the child participants in each study arm was comparable to that of the adult participants. Based on this information, we calculated the occlusion rate ratio for the

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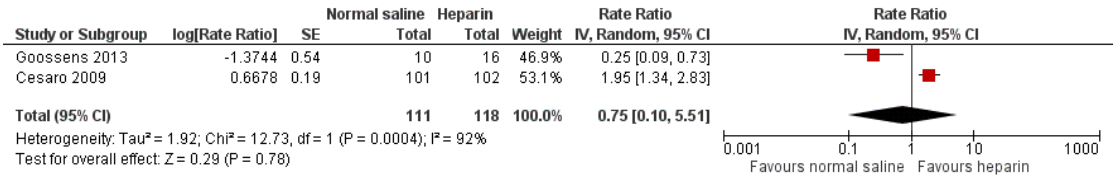
experimental arm (normal saline) versus the standard arm (heparin) for each study per 1000 catheter days. In both Smith 1991 and Cesaro 2009 there were more CVC occlusions in the experimental (normal saline) arm. The rate ratio of CVC occlusion in Smith 1991 was 2.0 (95% CI 0.18 to 21.85), and in Cesaro 2009 the rate ratio was 1.95 (95% CI 1.34 to 2.83). Goossens 2013 found there were fewer CVC occlusions in the experimental (normal saline) arm; the rate ratio was 0.25 (95% CI 0.09 to 0.73). Because of absent data regarding the first period in the cross-over study design used in Smith 1991, results from this study were not pooled. When the results from the Cesaro 2009 and Goossens 2013 studies were pooled, the heterogeneity was 92% (I^2 = 92%); the random-effects model was chosen to estimate the combined effect. While combined analysis suggested there was no statistical difference in the outcome of CVC occlusion between flushing with heparin or normal saline (rate ratio 0.75, 95% CI 0.10 to 5.51; participants = 229; studies = 2; Z = 0.29, P = 0.78), the heterogeneity between studies indicates this result may be due to differences between the studies. See Analysis 1.1 and Figure 4. We graded this evidence as very low quality (see Summary of findings for the main comparison).

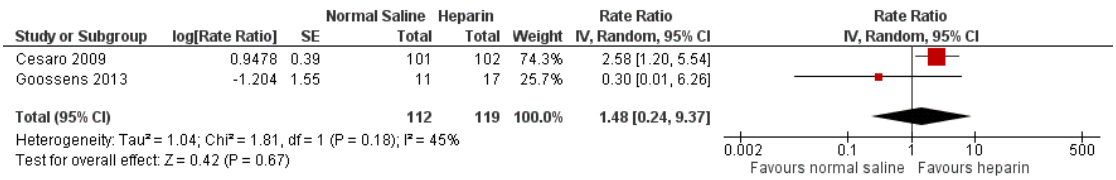
Figure 4. Forest plot of comparison: 1 Comparison: Normal saline versus heparin flush, outcome: 1.1 Outcome 1: CVC occlusion rate per 1000 catheter days.



CVC-associated blood stream infection or colonisation (Analysis 1.2)

Incidence of CVC-associated blood stream infection was reported in all three included trials (245 participants). As described above, rate ratios were calculated for each study based upon 1000 catheter days. There were more CVC-associated blood stream infections in the experimental (normal saline) arm in both Smith 1991 and Cesaro 2009 studies. The rate ratio in Smith 1991 was 2.00 (95% CI 0.18 to 21.85); in Cesaro 2009 the rate ratio was 2.58 (95% CI 1.20 to 5.54). In Goossens 2013, there were no incidences of infection in the experimental (normal saline) arm, therefore in order to calculate the log of the standard error for the rate ratio, as per section 9.4.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* , 0.5 was added to each arm of the study (Deeks 2011). The resulting calculation in Goossens 2013 was a rate ratio of 0.30 (95% CI 0.01 to 6.26). We pooled the results of Cesaro 2009 and Goossens 2013. The heterogeneity between studies was 45% (I^2 = 45). Because the I^2 statistic approached 50% and there was also evidence of clinical heterogeneity between the studies, (e.g. difference in frequency of flushing, implanted catheters and tunnelled catheters, use of positive pressure cap) the random-effects model was used. See Analysis 1.2 and Figure 5. There is no significant association between the use of saline to flush CVC and the incidence of CVCassociated blood stream infection (rate ratio 1.48, 95% CI 0.24 to 9.37; participants = 231; studies = 2; Z = 0.42, P = 0.67). We graded this evidence as low quality (see Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Comparison: Normal saline versus heparin flush, outcome: 1.2 Outcome 2: CVC-associated blood stream infection rate per 1000 catheter days.



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Duration of CVC placement (days)

After a median follow-up of 360 days, Cesaro 2009 reported that CVC survival was similar between the two study arms (203 participants). In the experimental (normal saline) arm mean survival was reported as 77% (95% CI 66% to 84%), and in the standard (heparin) arm mean survival was reported as 69% (95% CI 53% to 80%).

Duration of CVC placement was not reported in either Goossens 2013 or Smith 1991.

Secondary outcomes

Inability to withdraw blood from the CVC

Goossens 2013 reported on the inability to withdraw blood from the CVC (26 participants). Compared to the experimental (normal saline) group, there was a decreased inability to withdraw blood from the CVC in the heparin group, rate ratio 0.32 (95% CI 0.14 to 0.88). Cesaro 2009 and Smith 1991 did not report on the (in)ability to withdraw blood from the CVC.

Any use of urokinase or recombinant tissue plasminogen

Urokinase was used in 116 of 124 (94%) episodes of CVC occlusion in the Cesaro 2009 study of 203 patients, and patency was restored in 107 out of 116 (92%). No specific information was available regarding which treatment arm urokinase was used in and the subsequent result, however it is noted that 83 CVCs occluded in the normal saline group and 41 in the heparin group. Five of the CVCs were occluded in only one lumen and so were left in situ while the remaining four were unable to have patency restored in either lumen and were prematurely removed. There was no information available regarding the use of urokinase or other drugs to restore patency in either Goossens 2013 or Smith 1991.

Incidence of removal/re-insertion of the catheter

Cesaro 2009 reported premature removal of a CVC was required in 44 participants, 22% of the total study population of 203 patients. Premature removal was comparable between the two study arms, 21 in the saline arm and 23 in the heparin arm, and was generally indicated because of dislocation of the catheter or infection, rather than CVC occlusion. There was no information regarding this outcome from Goossens 2013 or Smith 1991.

Other CVC-related complications

Dislodgment of the CVC occurred in 38/203 (19%) of the total study population in Cesaro 2009. There were no statistical differences between study arms; rate ratio 0.87 (95% CI 0.46 to 1.63). In Smith 1991, dislodgement occurred in 2/14 (14%) of the study population. There was no statistically significant difference between study arms; rate ratio 0.2 (95% CI 0.01 to 4.81). There was no information regarding this outcome available from Goossens 2013.

CVC site infection was reported in 24/203 (12%) in Cesaro 2009 with no statistically significant differences between study arms; rate ratio 0.68 (95% CI 0.30 to 1.52). In Smith 1991 CVC site infection was reported in 6/28 (21%) of the study population, again there was no difference between study arms; rate ratio 7.0 (95% CI 0.37 to 132.4).

CVC-related thrombosis was reported in 2/203 (1%) of the study population in Cesaro 2009 with no differences between study arms; rate ratio 1.0 (95% CI 0.06 to 15.86). In Smith 1991, CVC-related thrombosis was reported in 2/14 (14%) of the population, again there was no difference between study arms; rate ratio 1.0 (95% CI 0.06 to 15.86).

There were no data available from Goossens 2013 regarding other CVC complications in the paediatric population of 28 patients.

Subgroup analysis

As there were only three studies included in this review, we were not able to undertake any subgroup analysis.

Sensitivity analysis

Due to the limited number of studies in this review, it was not appropriate to undertake a sensitivity analysis.

DISCUSSION

Summary of main results

This systematic review compared the use of heparin locks (standard care) with experimental use of 0.9% sodium chloride (normal saline) locks. The outcomes of interest were: CVC occlusion; CVC-associated blood stream infection; duration in days of catheter placement, inability to withdraw blood from the CVC; use of urokinase or recombinant tissue plasminogen; incidence of removal or re-insertion of the CVC, or both; dislocation of the CVC; other CVC infection; thrombosis associated with CVC; allergic reaction; haemorrhage; heparin-induced thrombocytopaenia, and elevated hepatic enzymes. Rate ratios were calculated for outcome measures to estimate the probability of each event occurring in each treatment arm. See Summary of findings for the main comparison for details on the primary outcomes CVC occlusion and CVC-associated blood stream infection. The quantity of the evidence was small; we were only able to include three studies and

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the results were inconsistent. We found that there is insufficient data to determine the effects of intermittent flushing of normal saline verus heparin to prevent CVC occlusion or CVC-associated blood stream infection in infants and children. The use of a positive pressure cap in Cesaro 2009 may have biased the results of this study regarding the outcome of CVC-associated blood stream infection; there is evidence of an association between the use of a positive pressure cap and CVC-associated blood stream infection in other studies (Jacobs 2004; Jarvis 2009; Marschall 2008). The quality and strength of the evidence for the use of normal saline instead of heparin for the routine management of CVC is low and further well designed studies are required.

Overall completeness and applicability of evidence

The trials included in the review directly compared the use of normal saline and heparin in long term central venous catheters in children in community and acute settings, and we were able to undertake two meta-analyses. All studies included participants representative of those usually found in the clinical setting. However, between studies, all used different protocols for the standard and experimental arms with different concentrations of heparin and different frequency of flushes reported. Additionally, within studies, Smith 1991 and Cesaro 2009 changed not only the solution being used, but also the frequency of flushes. Any difference seen could therefore be plausibly attributed to either the solution or the frequency of flushes; changing the frequency of flushes may actually confound the results towards the null hypothesis.

The three included studies employed a pragmatic approach to assess the effectiveness of saline in routine care. While this approach is desirable to inform policy and routine practice, greater emphasis is required to minimise bias and confounding in the study design to ensure generalisibility. As there are concerns with the internal validity of all three studies, the generalisibility (external validity) of results from the studies included in the review is poor.

Quality of the evidence

Study methodology

The assessment of bias for all studies was summarised using Cochrane's risk of bias tool (Figure 3) and indicated a high level of heterogeneity. There were methodological weaknesses in all studies. Because of the nature of the outcomes, it was not possible to blind participants or clinicians. However it could be argued that, if the frequency of flushes had been kept consistent between the experimental and standard arms, greater care could have been taken to blind the intervention from both participants and clinicians. Other concerns included the potential for selection bias, selective reporting bias and possible confounding of results.

The study undertaken by Smith 1991 in particular is subject to high levels of uncertainty regarding its precision. This study was undertaken many years ago and is reported with minimal detail. It is unclear how the data were analysed (i.e. paired or un-paired), or if individual participants experienced more than one outcome. Following this study, the institution where the study was conducted changed their practice, replacing heparin with normal saline locks. Recent communication with this institution (HHSC 2014 [pers comm]) confirmed that the facility continues to routinely use normal saline locks for long term CVCs in children over 12 months of age, providing strong support of the study's findings. Therefore despite the bias evident in this study, it is important to consider the clinical implications of the experience of the efficacy of normal saline locks in long term CVCs over two decades.

In the study reported by Cesaro 2009, the randomisation process is well reported and the study is methodologically sound. However there are concerns regarding the potential for outcomes to be attributed to the positive pressure cap, or the frequency of flushes (or a combination of both) and so it is unclear what role the flushing solution plays.

Goossens 2013 did not intend for the subset of paediatric data to be analysed separately; their study included a large number of adults and only a small proportion of children (28/802, 3.5%). As a consequence, not all the information required to make an assessment of the quality of the study was available.

Heterogeneity, inconsistency and imprecision of results

When we combined the two studies (Cesaro 2009; Goossens 2013) to assess the effect of normal saline on CVC occlusion, the heterogeneity was high. The combined results of both CVC occlusion and CVC-associated blood stream infection revealed wide confidence intervals (Analysis 1.1; Analysis 1.2) which included the null hypothesis. The studies do not appear to provide consistent information and we were unable to determine the precision of the studies. The small sample sizes and the few events in the two studies are likely the cause of this heterogeneity.

The overall quality of the evidence was assessed as very low to low using the GRADE assessment tool; there was a high risk of performance and detection bias in all studies as well as a high risk of other bias related to differences in frequency of flushes between heparin and saline groups in Cesaro 2009 and Smith 1991. A high risk of other bias is also assumed for the subset of unpublished paediatric data provided for Goossens 2013. In addition we identified heterogeneity, imprecision and inconsistency of the effect estimates. Consequently, the significance of the results of these meta-analyses should be interpreted with caution. Further research is likely to improve the confidence in the estimate of these effects if undertaken with greater attention to methodology.

Potential biases in the review process

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None of the review authors were investigators in any of the studies included in this review. The literature review was thorough and the methodology transparent and can be reproduced. None of the review authors had any conflicts of interest to declare. While we attempted to minimise bias in this review as described above, we are aware that there are differing practices worldwide and there may be unpublished studies which were not included in this review. The review authors made assumptions with the paediatric data provided in the Goossens 2013 study that the subset of paediatric patients had the same catheter days at risk as reported in the larger study; these assumptions may have introduced bias in the review process. We originally defined the study population as children and infants aged 1-18 years. The included studies had recruited children from aged 0 - 20 years, accordingly we changed our study population to include these ages as there was not enough data available to exclude children aged under 1 year in Cesaro 2009 or over 18 years in Smith 1991; we made the assumption this was unlikely to effect the results.

Agreements and disagreements with other studies or reviews

A recent systematic review (Conway 2014) concurred with our findings that there is insufficient evidence to support the use of normal saline to prevent CVC occlusion. This review included studies related to the adult population and also peripherally inserted CVCs. Conway 2014 concluded with recommendations for daily flushing with heparin based on the practices of selected facilities. However, there is insufficient evidence to make this recommendation and this recommendation may lead to higher amounts of heparin being used than is necessary, introducing avoidable costs and risks associated with the use of heparin in this patient group. Peripherally inserted CVCs have a much narrower lumen and require different care and thus were excluded from this Cochrane Review.

There are numerous observational studies that investigate this issue (Bowers 2008; Fratino 2005). Many of these studies support the use of normal saline for routine flushing of long term CVCs (Abate 2013; Kelly 2008) and institutions report the practice of using normal saline in their clinical practice guidelines (Nelson 2008). Despite the literature suggesting that heparin may not be required to maintain patency of CVCs, more RCTs are required to determine the ideal flush solution, concentration, and the frequency of flushes (Baskin 2009). Without strong evidence to support the use normal saline, debate will continue and inconsistencies in practice will prevail. In an area where patients are already vulnerable as a result of their disease state, there should be greater understanding of this relatively simple question and practice should be standardised.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine the effects of intermittent flushing of heparin versus normal saline to prevent occlusion in long term central venous catheters in infants and children. It remains unclear whether heparin is necessary to prevent occlusion or CVC-associated blood stream infection. Controversy between institutions around the world regarding the appropriate care and maintenance of these devices remains.

Implications for research

Given the results of this review, there is a need for healthcare organisations to consider undertaking further research in this area to contribute to the evidence base. Ultimately this would facilitate the development of evidence-based clinical practice guidelines and consistency of practice. Careful attention to study design is required, including blinding and proper sample size calculations to detect clinically meaningful differences, and ensuring only one aspect of the intervention is changed in the experimental arm (flushing frequency, concentration of heparin or use of normal saline). Such studies would generate evidence and ensure results could be appraised and generalised to address the current gaps in knowledge. Consistency of outcome reporting would aid interpretation of results. No studies measured the costs associated with standard or experimental treatment; cost analysis would be a useful addition to future studies. Alternatively, decision models could be used to ascertain what differences in complication rates would make a meaningful difference in costs or outcomes.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cesaro 2009

Methods	**Study design:** prospective parallel randomised controlled study, at a single tertiary referral centre, during a 25-month study period **Method of randomisation:** computer generated **Allocation of concealment:** sealed envelopes
Participants	**Country**: Italy **Setting:** single tertiary referral centre **Numbers:** 203 paediatric haematology or oncology patients with tunnelled Broviac CVC. 101 participants randomised to experimental treatment and 102 participants randomised to standard treatment group **Age:** 0 to 17 years, age < 5 years = 39, age > 5 years = 62 in experimental group; age < 5 years = 41, age > 5 years = 61 in standard treatment group **Gender:** 60 male, 41 female in experimental group; 60 male, 42 female in standard treatment group **Catheter days at risk:t**Total of 75,249 catheter days. Mean of 381 days per person (range 11 to 1072) in the experimental group; 351 days per person (range 4 to 1073) in the standard treatment group **Inclusion criteria:** paediatric patient (0 to 17 years of age, with malignant or non-malignant haematologic or oncologic disease with a Broviac-Hickman-type CVC- i.e. tunnelled, partially inserted, open-ended, inserted for the purpose of chemotherapy of haematopoietic stem cell transplantation **Exclusion criteria:** not stated
Interventions	**Experimental treatment group:** flushing with normal saline at least weekly via a positive pressure cap **Standard treatment group:** flushing with 3 mL of normal saline with 200 units heparin twice weekly via a standard CVC cap
Outcomes	• Incidence of CVC complications: occlusion, dislocation of CVC, CVC-related infection, exit site infection, thrombosis • CVC survival (weeks) • Organisms isolated from blood cultures
Notes	Potential confounding of results due to outcomes being attributable to positive pressure cap or frequency between flushes rather than the flushing solution used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "Computer generated randomisation lists were drawn up by a statistician not involved in patient management"

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Cesaro 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	**Quote:** "Stored by sequentially numbered sealed envelopes. Permuted blocks of four were used for treatment allocation. Information concealed to investigators until completion of recruitment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** no blinding of participants or personnel. Different caps were used in the different arms of the study
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** due to nature of outcomes, not possible to blind assessment of outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** low attrition rate, follow up for median of 360 days, results from all enrolled participants were reported
Selective reporting (reporting bias)	Unclear risk	**Comment:** all nominated outcome data were reported. No study protocol available
Other bias	High risk	**Comment:** outcomes could also be attributed to different caps, or frequency of flushing, not only to use of different solutions

Goossens 2013

Methods	**Study design:** prospective parallel randomised controlled trial, at a single tertiary referral centre, during a 23-month study period **Method of randomisation:** computer generated **Allocation of concealment:** sequentially numbered cards located in a separate area
Participants	**Country:** Belgium **Setting:** single tertiary referral centre **Numbers:** 802 individuals with an oncology or haematology condition, who had a totally implantable intravenous catheter inserted. A subset of unpublished data was obtained from the investigators for 28 (3.5%) participants, aged one to 18 years of age; 11 participants were randomised to experimental treatment group and 17 were randomised to standard treatment group. No further details available for paediatric subset of data **Age:** 1 - 71 years, mean age 57.9 years (SD 14.8) in experimental group; mean age 54.9 years (SD 16.6) in standard treatment arm. Further details not available for paediatric subset **Gender:** 261 (64.6%) female in experimental group, 263 (66.1%) female in standard treatment groups. Further details not available paediatric subset **Catheter days at risk:** total catheter days 115,991: 58,197 in the experimental treatment arm (mean 152.4 days per patient); 57,794 in the standard treatment arm (mean 150.9 days per patient). The assumption was made that the mean catheter days was equivalent

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	in the paediatric population **Inclusion criteria:** patients older that one year of age, scheduled for insertion of a totally implantable central venous catheter for the first time, with a haematology or oncology condition and expected to survive for the planned follow up of 180 days **Exclusion criteria:** patients (or caregivers in the case of children) unable to provide informed consent, unable to stand for a post-operative chest X-ray, patients with therapeutic intravenous heparin administration, a history of HIT or abnormal clotting tests, or coincident participation in other clinical trials
Interventions	**Experimental treatment group:** pulsatile flushing with 10 mL of normal saline and then locking with positive pressure **Standard treatment group:** pulsatile flushing with 10 mL of normal saline, followed by 3 mL heparin (100 units/mL) and locking with positive pressure
Outcomes	• Rate of inability to aspirate blood while injection was easy (assessed at every access) • Incidence of CVC-associated blood stream infection • Incidence of functional problems associated with CVC
Notes	Subset of paediatric data (unpublished) was obtained to assess outcomes for children only: 26 out of 28 children contributed data. Not all variables available, there may be some systematic differences in the characteristics of children in the subset of data, the study was not powered to analyse this subset of data separately

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "We randomly assigned patients in a 1:1 ratio using computerised random numbers to two groups"
Allocation concealment (selection bias)	Low risk	**Quote:** "The allocation sequence was concealed from researchers who enrolled patients according to sequentially numbered patient cards stored in a separate room." Patients were assigned to groups following providing consent to participate
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** due to nature of outcomes, it was not possible to blind the assessment of outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**Comment:** attrition occurred with adult participants, however analysis was based on CVC access rate rather than individual pa-

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		tient data. Unsure if paediatric data was complete
Selective reporting (reporting bias)	Unclear risk	**Comment:** all nominated outcome data were reported. No study protocol available
Other bias	High risk	**Comment:** subset of paediatric data was unpublished, provided by the study author; there may be systematic differences of participant characteristics in this subset of data

Smith 1991

Methods	**Study design:** prospective cross-over randomised controlled trial, at a single tertiary referral centre, during a seven month study period **Method of randomisation:** no information available **Allocation of concealment:** no information available
Participants	**Country:** Canada **Setting:** single tertiary referral centre **Numbers:** 14 participants with tunnelled Broviac CVC **Age:** 21 months to 20 years of age (median 5.4). As a cross-over design, the same participants were in both the experimental treatment group and the standard treatment group **Gender:** no information available **Mean duration of catheter days at risk:** total catheter days 3029: 1515 catheter days (mean 108 days per person) in experimental arm and 1514 (mean 108 days per person) in the standard arm **Incusion criteria:** none stated. All patients had CVCs placed prior to entering study **Exculsion criteria:** none stated
Interventions	**Experimental treatment group:** once per week flush with 9 mL normal saline **Standard treatment group:** twice daily flushes with 5 mL heparinised normal saline (10 units/mL heparin)
Outcomes	• Thrombosis formation at baseline, cross over point (14 weeks) and end of study (28 weeks) as measured by echocardiogram or inability to infuse or withdraw from CVC (occlusion) • Incidence of CVC mechanical issues (leak, migration) • Incidence of CVC-associated infection
Notes	Older study, not reported using contemporary standards. Potential for confounding of results due to outcomes being attributable to frequency between flushes rather than solution used. No information available for first cross-over period results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Smith 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	**Comment:** no information provided regarding sequence generation for randomisation; cross-over design but no information regarding how participants were selected **Quote:** "patients were randomised to one of two methods of catheter care and then crossed over at the end of a three and a half month period to the opposite arm for an additional three and a half month period"
Allocation concealment (selection bias)	Unclear risk	**Comment:** no information provided regarding allocation concealment, however as a cross-over design all participants were their own controls
Blinding of participants and personnel (performance bias) All outcomes	High risk	**Comment:** no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	**Comment:** due to nature of outcomes, not possible to blind assessment of outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** no attrition in study, results from all enrolled participants reported
Selective reporting (reporting bias)	High risk	**Comment:** all nominated outcome data reported in basic format, no results from statistical tests reported. It is not clear if paired analysis was undertaken. No study protocol available
Other bias	High risk	**Comment:** unable to establish if authors considered carry-over effect of the interventions from one arm to the other; possible selection bias. Outcomes could also be attributed to alterations between the frequency of flushes

CVC: central venous catheter
HIT: heparin-induced thrombocytopenia
SD: standard deviation

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
De Neef 2002	Type of catheter not relevant
Geritz 1992	Type of catheter not relevant
Kaneko 2004	Population not relevant - adults aged over 18 years
Pumarola 2007	Type of catheter not relevant
Rabe 2002	Type of catheter not relevant and population aged over 18 years
Schultz 2002	Type of catheter not relevant

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DATA AND ANALYSES

Comparison 1. Heparin versus normal saline flushing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CVC occlusion rate per 1000 catheter days	2	229	Rate Ratio (Random, 95% CI)	0.75 [0.10, 5.51]
2 CVC-associated blood stream infection rate per 1000 catheter days	2	231	Rate Ratio (Random, 95% CI)	1.48 [0.24, 9.37]

ADDITIONAL TABLES

Table 1. Rate per 1000 catheter days for primary and secondary outcomes

	Smith 1991		Cesaro 2009		Goossens 2013	
Outcome	**Normal Saline**	**Heparin**	**Normal Saline**	**Heparin**	**Normal Saline**	**Heparin**
CVC occlusion rate per 1000 catheter days	1.32	0.66	2.16	1.11	2.62	10.35
CVC-associated blood stream infection rate per 1000 catheter days	1.32	0.66	0.62	0.24	0.32	1.04
Inability to withdraw blood	Not reported	Not reported	Not reported	Not reported	3.42	10.60
CVC dislodgement	0.33	1.65	0.47	0.54	Not reported	Not reported
CVC site infection	2.31	0.33	0.26	0.38	Not reported	Not reported
CVC-related thrombosis	0.66	0.66	0.30	0.30	Not reported	Not reported

CVC: Central venous catheter

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CONTRIBUTIONS OF AUTHORS

All authors contributed to the design and development of the Cochrane protocol and participated in the review.

NB: contributed to study selection, appraisal, data extraction, data analysis and the writing of the review

RE: contributed to study selection and appraisal, and editing drafts of the review

RC: contributed to study appraisal, data extraction, data analysis and editing drafts of the review

DECLARATIONS OF INTEREST

NB: none known

RE: none known

RC: none known

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Internal sources

- Royal Children's Hospital, Queensland, Australia.

Royal Children's Hospital provided salary and facilities for NB and RE to conduct this systematic review.

- Royal Brisbane and Women's Hospital, Queensland, Australia.

Royal Brisbane and Women's Hospital provided salary and facilities for RC to conduct this systematic review.

- The University of Queensland's Centre for Online Health, Australia.

The Centre for Online Health provided salary and facilities for NB to conduct this systematic review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The duration of catheter placement was changed from number of weeks in the protocol, to number of days in the review as per the reported outcomes in the included studies' reported outcomes.

A secondary outcome measure of dislocation of CVCs was included in the review as it was deemed an important clinical variable.

We originally planned to use odds ratios or risk ratios in the published protocol, however outcome measures were not reported consistently in studies. As all included studies reported the number of catheter days for each study population, we were able to calculate rate ratios as a common metric to compare and report outcomes.

We originally defined the study population as children and infants aged 1 to 18 years. The included studies had recruited children from aged 0 to 20 years, accordingly we changed our study population to include these ages as there was not enough data available to exclude children aged under one year in Cesaro 2009 or over 18 years in Smith 1991; we made the assumption this was unlikely to effect the results.

We have included a 'Summary of findings' table and GRADE assessment of the evidence according to current Cochrane guidelines.

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